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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,541	ESHLEMAN ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10-13,23,28-30,40-42,75 and 76* is/are pending in the application.

4a) Of the above claim(s) *1-5,23,28-30,40-42,75 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6, 10-13, 23, 28-30, 40-42, 75 and 76 are pending.

Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn from examination as detailed in the previous Office Action.

Claims 6 and 10-13 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 03/23/2009. Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 1st ¶ - Written Description, New Matter

1. Claims 6 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 6 and 10-13 require detection of an alteration in the KRAS2 gene wherein the alteration 'encodes a G35A amino acid substitution', as recited in independent claim 6. However, with regard to the 'G35A', the specification as originally filed clearly indicates that this term denotes a G to A nucleotide substitution at position 35 in the

cDNA (where the A of the ATG start codon is position 1). The specification as originally filed does not appear to provide support for detection of a alteration in the KRAS2 gene that is a G35A amino acid substitution, which would require an alteration resulting in the substitution of an alanine amino acid in the place of a glycine amino acid at position 35 in the protein sequence. As such, the limitation of 'G35A amino acid substitution' as recited in independent claim 6 is considered new matter.

Withdrawn Claim Objections

2. The objection to claim 8 for recitation of non-elected subject material in the alternative, as set forth on page 2 of the Office Action of 12/16/2008, is **WITHDRAWN** in light of the amendments to the claims including the cancellation of claim 8. Applicants have elected for the examination of claims in so far as they require the specific KRAS2 mutation 'G35A'. No claim is yet indicated allowable. Prior to the allowance of the objected to claim, if non-elected subject matter is not rejoined, the non-elected subject matter will be required to be deleted from the claim.

Withdrawn Objection to the Specification - Sequence Compliance

3. The objection to the specification for failure to comply with the sequence rules, as set forth on page 3 of the Office Action of 12/16/2008, is **WITHDRAWN** in light of the amendments to the specification and the provided sequence listing of 03/23/2009.

Withdraw Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

4. The rejections of claims under 35 USC 112 2nd ¶, as being indefinite, as set forth on pages 4-5 of the previous Office Action of 12/16/2008, are **WITHDRAWN** in light of the amendments to the claims and the cancellation of claims.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 6 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

> A method of differentiating pancreatic cancer from chronic pancreatitis in a human subject, said method comprising:
> obtaining a biological sample from said human subject, said sample comprising nucleic acids from said subject;
> hybridizing said nucleic acids with at least one oligonucleotide pair to form a reaction mixture; wherein said oligonucleotide pair comprises a first oligonucleotide and a second oligonucleotide; wherein said first oligonucleotide comprises a first gene specific region and a first primer region, and said second oligonucleotide comprises a second gene specific region and a second primer region; wherein either said first oligonucleotide or said second oligonucleotide specifically hybridizes to the nucleotide sequence encoding the A allele of the G35A nucleotide mutation in the KRAS2 gene, said G35A nucleotide mutation encoding the G12D KRAS2 amino acid substitution; and wherein said first oligonucleotide said second oligonucleotide are suitable for ligation to one another;
> subjecting the reaction mixture to a ligation reaction to form a ligation product;
> amplifying said ligation product to form a reaction product;
> detecting said reaction product, wherein detecting said reaction product indicates the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject;
> wherein the presence of said A allele of the G35A nucleotide mutation in the KRAS2 gene in said nucleic acids from said subject is indicative of an increased likelihood of the presence of pancreatic cancer in said subject.

does not reasonably provide enablement for the breadth of the method as claimed which encompasses analysis of samples in any subject organism, and the detection of a nucleotide difference that encodes a G35A amino acid substitution, as recited in claim

6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to methods of differentiating pancreatic cancer from chronic pancreatitis using a particular amplification methodology to detect nucleotide content.

The claims encompass the analysis of any subject organism.

The invention thus requires knowledge of a correlative association between a nucleotide difference that encodes a G35A amino acid substitution in the KRAS2 gene in any organism and the presence of either pancreatic cancer or chronic pancreatitis.

Direction provided by the specification and working example

The instant specification provides examples (e.g. pages 76-91) of the analysis of KRAS2 mutations in human patients with either pancreatic cancer on non-cancerous pancreatic disorders. The specification provides, consonant with the election, the analysis of (see for example p.12 p.89) a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid (this nucleotide mutation is known in the art as the G12D mutation). The specification provides that the presence of the G12D encoding mutation is indicative of pancreatic cancer as opposed to benign disease (for example Table 4, p.91).

The specification does not provide for the association of any G35A amino acid substitution with the presence of pancreatic cancer or any other pancreatic disorder; nor does the specification provide for any nucleotide content (other than the G12D amino acid substitution caused by a GGT to GAT mutation in codon 12) as a G35A mutation.

The specification does not provide for any analysis of any non-human subjects.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art in detecting variable nucleotide content at any known mutation hot spot is high, the unpredictability in associating any nucleotide content with any particular phenotype, or extrapolating variable nucleotide content from any one organism to any other different organism is higher. The high level of unpredictability is demonstrated by the prior art.

The claims require differentiating pancreatic cancer from pancreatitis comprising detecting nucleotide difference that encodes a G35A amino acid substitution, asited in claim 6. The specification teaches only the analysis of (as consonant with the Election) a specific KRAS2 gene mutation identified as G35A (a G to A mutation at nucleotide position 35 of the KRAS2 cDNA, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid (this nucleotide mutation is known in the art as the G12D mutation) in human subject.

It is thus relevant to point out the unpredictability in extrapolating the presence of polymorphic nucleotide content, or its association with any phenotype, form one animal to any other different animal. Such unpredictability in interspecies extrapolation is

addressed by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Additionally, Hacker et al (1997) teaches that they were unable to confirm an association between particular variable nucleotide content and a phenotype (i.e. the phenotype of ulcerative colitis) in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Thus it is highly unpredictable as to whether or not the analysis of any nucleotide content, as encompassed by the specification, would be reliably associated with either pancreatic cancer or chronic pancreatitis.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention in the full scope of the claims. Within the scope of the claimed invention one would have to perform experimentation to identify in any non-non human subjects any nucleic acid content that is particularly indicative of either pancreatic cancer or chronic pancreatitis. Even if one were to perform such experimentation, there is no assurance that any other reliable associations, beyond those identified earlier in this rejection (i.e. as consonant with the election, a specific KRAS2 gene mutation identified as G35A (a G to A mutation at position 35, where the A of the initiator ATG is position 1) which changes codon 12 from GGT to GAT, changing amino acid 12 from glycine to aspartic acid) as enabled by the instant specification would be found.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the specific working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the claimed invention in the full scope as encompassed by the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement in the full scope encompassed by the claims. Applicants' arguments have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants have argues (p.14 of the Remarks) that the claims have been amended to included the limitations that are indicated as enabled in the rejection. However, in examining the limitations of the claims it is noted that the rejection has set forth that the enabled subject matter includes limitations regarding the analysis of human subjects, and the detection of the A allele of the particular G35A nucleotide substitution as indicative of the presence of pancreatic cancer in a subject. These limitations have not been addressed in the amendments to the claims.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections - 35 USC § 102

7. The rejection of claims under 35 USC 102 as anticipated by Schouten et al, as set forth on pages 10-11 of the previous Office Action, is **WITHDRAWN** in light of the amendment to the claims. As such Applicants remarks with regard to the withdrawn rejection are moot.

Maintained Claim Rejections - 35 USC § 103
Newly applied to claims as necessitated by amendments

8. Claims 6 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Maire et al (2002) and Lecomte (2002).

With regard to the limitations of claim 6, Schouten et al (summarized in Fig.2 on p.4, and Fig 8 on p.11) teaches a method that comprises contacting a nucleic acid sample with a pair of oligonucleotides in which each of the oligonucleotides has a gene specific region (termed 'hybridisation sequence' in the reference) and a primer region (termed 'PCR primer sequence Y' and 'PCR primer sequence X' in the reference). The reference indicates that mutation detection can be accomplished by using a nucleotide difference (as compared to the target nucleic acid sequence) in the gene specific region of one oligonucleotide (p.11, right col., lns.5-10). The method steps of the reference indicate that the primers of the pair are suitable for ligation to one another (p.2, right col., ln.1). Furthermore the reference teaches a ligation reaction and amplification of the formed ligation product (p.2, right col., ln.1-23). The reference teaches analyzing the reaction product (Fig 3).

Schouten et al does not specify the analysis of a G35A KRAS mutation, nor that a G35A KRAS mutation is indicative of a phenotype.

However, the analysis of a G35A mutation in KRAS2 and its association with pancreatic cancer was well known in the art at the time the invention was made.

Maire et al teaches the analysis of mutations in differentiating between pancreatic cancer and chronic pancreatitis.

Relevant to claims 6, 10, and 13, Maire et al teaches the analysis of G12D mutations in codon 12 of the KRAS2 gene (p.552 – Detection of KRAS2 gene mutations). Relevant to the limitations of claim 6, the mutation analyzed by the allele specific amplification of Maire et al is the same G35A mutation of the instant specification, as evidenced by Lecomte et al (Table 1). Relevant to claims 10 and 13, the analysis of allele specific amplification products is determining a KRAS mutation level (relevant to claim 10) and analysis of mutations in subjects is monitoring KRAS mutation levels (relevant to claim 13).

Relevant to the limitations of claims 11 and 12, Maire et al teaches that the presence of the KRAS2 G35A mutation is indicative of pancreatic cancer as opposed to chronic pancreatitis (p.552 – KRAS2 mutations in circulating DNA; p.551 - Abstract). With regard to the limitations of claims 11 and 12, the teachings of Maire et al indicate that a mutation level of 0.0% (e.g. undetected KRAS2 mutation) is indicative of chronic pancreatitis (claim 11), and a mutation level of 100% (e.g. KRAS2 mutation detected in all samples from a subject) is indicative of pancreatic cancer (claim 12).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Schouten et al for the analysis of the KRAS2 G12D mutation as taught by Maire et al to be indicative of the presence of pancreatic cancer. One would have been motivated to analyze the mutation of Maire et al based on the assertion of Maire et al that such an analysis is useful as a cancer diagnostic (p.553, right col., last paragraph).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the cited prior art. Applicants' arguments have been fully and carefully considered but are not found to be persuasive. Applicants have argue that independent claim 6 has been amended to include the subject matter of previously presented claim 9 (i.e. the limitation that a reaction product is analyzed). It is noted that this specific limitation was previously rejected under 35 USC 102 as anticipated by the teachings of Schouten et al (p.11 of the Office Action of 12/16/2008). As necessitated by the amendments to the claims, the rejection of claims under 35 USC 102 as anticipated by the prior art have been withdrawn, and a such the newly set forth rejection of the amended claims is required.

The rejection as set forth is **MAINTAINED.**

Conclusion

9. No claim is allowed. No claim is free of the teachings of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date

of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Art Unit 1634